#25

PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ram PRATAP, et al

Serial No.: 09/316,313 Group No.: 1625

Filed: May 21, 1999 Examiner: E. Huang

For: METHOD FOR THE TREATMENT OF MALARIA BY THE USE OF PRIMAQUINE DERIVATIVE N^1-(3-ETHYLIDINOTETRAHYDR-2-ONE)-N^4-(6-METHOXY-8-QUINOLINYL)-1,4-P0ENTANEDIAMINE AS GAMETOCYTOCIDAL AGENT

Attorney Docket U-012254-3

Commissioner Patents and Trademarks
Washington, DC 20231

APPEAL BRIEF

Sir:

(1) Real Party in Interest

The real party in interest for this application is the Council of Scientific and Industrial Research, the assignee of the entire right, title and interest in and to this application.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, DC 20231

CLIFFORD J. MASS
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Date: January 28, 2002

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(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 11-20 have been finally rejected and are the subject of this appeal. Claims 1-10 and 21 were canceled previously.

(4) Status of Amendments

The amendment requested in the Amendment After Final filed 23 July 2001 has been entered, as courteously noted in the Advisory Action dated August 9, 2001. A Second Amendment After Final is being submitted simultaneously with this Appeal Brief and (obviously) has not been entered or considered on the record.

(5) Summary of Invention

The invention is a method for treatment of malaria or for combating malaria hypnozooites in the liver of an animal which comprises administering to an animal a therapeutically effective amount of the compound described in the specification at page 1, first full paragraph (identified as "the compound of formula 1") or a composition comprising the compound of formula 1. The compound has an enaminone functionality with gametocytocidal activity and low toxicity (see specification at page 11, last paragraph; pages 14-15 and Tables I and II on pages 18-20 (showing

gametocytidal activity); and pages 15-16 and Tables IV-V on pages 21-23 (showing low toxicity)).

(6) Issue

Whether claims 9-20 are unpatentable under 35 USC 103 over Andersag US Patent 2,187,847?

(7) Grouping of Claims

The claims do not stand or fall together. As discussed in Section (8) *infra*, claims 12 and 13 are separately patentable, and the claims depending from claim 16 are also separately patentable.

(8) Argument

a) Background

There has been a long-felt need for a primaquine derivative that has enhanced antimalarial activity and yet overcomes the longstanding problem posed by the toxicity of primaquine. In the present case, the evidence of record in the specification and in literature references cited of record establish a long-felt need for a primaquine derivative that has enhanced anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of primaquine. This problem is described in the specification of the present application at, for example, the paragraph bridging

pages 2 and 3 of the specification. Moreover, Appellant respectfully calls attention to the Saxena et al article cited in the Information Disclosure Statement dated November 1, 2000 which states in pertinent part:

> "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system such as induction of methaemoglobinaemia, haemolytic anaemia in G-6-PD deficient cases and toxicity in pregnant woman. Primaquine and other 8-aminoquinolines, are also known to produce oxidative stress, and inhibit various components of hepatic microsomal mixed function oxidase (MFO) system both *in vivo* and *in vitro*." (References omitted.)

Appellant also calls attention to the fact that the need for a solution to the problem exists more than sixty (60) years after issuance of the Andersag patent!

As discussed in the specification, the claimed method satisfies the long-felt need for a solution to the problem. The specification shows an enhanced gametocytocidal activity of the claimed compound (see specification at pages 14 - 15 and Tables I - II) and a reduced toxicity in methaemoglobin and glutathione tests (see specification at pages 15 - 16 and Tables IV - VI). The specification thus shows the enhanced effectiveness of the claimed compound as compared with "the most important member of the 8-aminoquinoline group" (see Saxena et al excerpt above).

b) The Cited Art Does Not Establish a Case of *Prima Facie* Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in a reference or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on an applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991). It is respectfully submitted that these criteria are not met in the present case, as discussed below.

i) The Cited Art Does Not Teach or Suggest All of the Claim Limitations

Appellant first notes that the cited reference, Andersag, does not describe the recited compound of formula 1. The Examiner acknowledges this, but argues that Andersag teaches a genus that encompasses the compound of formula 1 and includes, as one of twelve working examples, an example (Example 11) of the preparation of a specific compound that is allegedly structurally similar to the compound of formula 1. Example 11 describes the condensation of several different compounds, none of which results in the claimed compound. The closest compound described in Example 11 is the one described at page 2, second column, lines 45 - 48. This compound differs from the claimed compound in a number of significant respects. First, the cited compound has a pentane portion with the amino group in the 8 position of the amino functionality bound to a $CH(CH_3)$ group. By contrast, the reference compound would have the amino group in the 8 position of its amino functionality bound to a CH_2 group rather than to a $CH(CH_3)$ group. This would clearly affect the properties of this amino position. Moreover, the reference compound would have a lactone group with a beta methyl substituent that is lacking from the claimed compound.

ii) There is No Motivation to Modify the Reference

The Examiner nevertheless contends that Andersag provides motivation for one of ordinary skill in the art to modify the compound of Example 11 to arrive at the compound of formula 1 (and to use this compound in a method to treat malaria) because the reference allegedly teaches that any species within the disclosed genus would be effective in treating malaria. As discussed below, Appellant respectfully disagrees with the Examiner's contention that Andersag teaches that **any** species within the disclosed genus would be effective in treating malaria. Nevertheless, even assuming for the sake of argument that this contention were true, the reference would still not provide the required motivation to modify the compound of Example 11 as next discussed.

An indication that all compounds within a described genus would have antimalarial effects would not provide a motivation to select any particular compound from within the genus as opposed to any other. It certainly would not provide a motivation to substitute an amino-methyl-butyl- amino for an amino n-pentyl-amino or to remove a methyl from a butyrolactone as would be required to arrive at the compound of formula 1 from the reference compound. Indeed, if the inclusion of the reference compound in Example 11 were considered as an indication that such compound is one that is preferred, why would one of skill in the art have a motivation to replace or modify its substituents at all? Moreover, why would one of skill in the art be motivated to make the proposed substitutions as opposed to the myriad other substitutions that are possible within the framework of the generic formula described in Andersag and the other Andersag examples? The answer is that one of skill in the art would <u>not</u> be motivated to make these substitutions especially since Andersag's description relates generally to condensation

products of acetylbutyrolactones and primary amines of the aromatic and heteroaromataic series and not to enaminone derivatives of primoquine of the 8-aminoquinoline class. Appellant respectfully submits that Andersag provides no motivation to make the modification proposed by the Examiner.

In the absence of a motivation in the reference to select the recited compound of formula 1 from the vast number of compounds encompassed by the generic formula described therein, the reference cannot be considered to set forth even a *prima facie* case of obviousness (see *In re Baird*, 29 USPQ 2d 1550, 1552 (Fed. Cir. 1994)). The mere fact that the reference **can** be modified does not render the proposed modification obvious in the absence of a suggestion in the reference of the desirability of the modification (see *In re Mills*, 16 USPQ 2d 1430 (Fed. Cir. 1990); see also MPEP Section 2143.01).

iii) The Cited Art Does Not Provide a Reasonable Expectation of Success in the Claimed Method

Even assuming for the sake of argument that one of ordinary skill in the art would be motivated to modify the compound of Andersag Example 11 as contended by the Examiner, there still would not be a reasonable expectation of success in practicing the claimed method as would be required to establish a *prima facie* case of obviousness. In this connection, Appellant respectfully calls the Examiner's attention to the specification at pages 6 - 9, wherein the therapeutic activity and the toxicity of primaquine and its metabolites are discussed. The specification shows clearly the unpredictability in this art and the effect of small structural changes on the biological activity of primaquine and its derivatives. Given this unpredictability,

Appellant respectfully submits that one of skill in the art could not have had even a reasonable expectation from Andersag that the claimed compound (a) could be safely administered to a patient in any dosage, and (b) could be effective in treating the patient against malaria (see *Ortho Pharmaceutical Corp. v. Smith*, 22, USPQ 2d 1119, 1125 (Fed. Cir. 1992)).

The above is especially true in view of the limited disclosure in Andersag and the contradictory disclosure of the prior art as a whole. In this connection, it is axiomatic that each prior art reference must be evaluated as an entirety, and all of the prior art must be evaluated as a whole (see, e.g., *In re Evanega*, 44 USPQ 2d 1249 (Fed. Cir. 1987)). When considering Andersag as an entirety, it must be recognized that the reference contains only a passing reference to usefulness of the entire class of described compounds in the treatment of malaria. This does not mean, nor would it be taken by those of skill in the art to mean, that each and every compound within the described genus (nor even each and every compound exemplified in the patent) would be useful against malaria parasites. Moreover, the general statement of usefulness in the Andersag reference must be considered in the context of the prior art as a whole. As can be gleaned from the references cited in the specification at pages 6 - 9, and as discussed above, one cannot generalize as to the effectiveness or toxicity of primaquine or its derivatives. Indeed, the prior art when considered as a whole, teaches the opposite, i.e., generalization is impossible. Moreover, the evidence of unsolved need (discussed below) belies any implication that all compounds embraced by the Andersag genus would be useful to treat malaria.

Andersag does not discuss or even recognize differences between the biological activity or toxicity of any of the compounds described therein. When considered as a whole, the reference would not motivate one of skill in the art to make the recited compound with even a

reasonable expectation that it would be therapeutically effective in treating malaria with low toxicity. The salient points are as follows:

i) Andersag relates to condensation products of acetylbutyrolactones and primary amines of the aromatic and heteroaromatic series. The patent does not disclose any biological activity of the amines used or their toxicity. The only disclosure relates to the reaction with therapeutically useful amines.

ii) Primaquine, of which the compound of formula (1) of the invention is a derivative with an enamionone functionality, itself and its toxic metabolites were developed much subsequent to the Andersag Patent. The specification of the present application provides a detailed description of prior art which includes disclosure of primaquine and its toxic metabolites.

iii) Insofar as the Examiner's observations regarding the inherency of the gametocytocidal activity, low toxicity, controlled delivery facilitation, etc. are concerned, neither Andersag nor the aforementioned prior art described in the specification would provide even a reasonable expectation that putting enaminone at the terminal nitrogen atom would result in the slowing down of chain degradation, reduce methaemoglobin formation thereby lessening toxicity, or provide lower toxicity in terms of increased levels of glutathione. As is clear from the prior art, the high toxicity of primaquine affected its use as an antimalarial agent despite its otherwise demonstrable activity in terms of blood schizontocidal, tissue schizontocidal and gametocytocidal activity. The prior art metabolites of primaquine were either non-functional, or also responsible for its toxicity. The same would have been expected of the Andersag compounds.

iv) There is no teaching in the prior art that putting enaminone at the terminal nitrogen atom would lower the levels of oxidation of glutathione and reduce the levels of methaemoglobin formation thereby lessening toxicity.

v) Also, as is demonstrated in the specification on page 16, last paragraph, the use of primaquine *per se* causes drug induced haemolysis in persons deficient in G-6PD enzyme. The use of the compound of formula I of the invention, does not cause this result.

vi) The prior art does not show or suggest the enhanced or improved gametocytocidal activity of the compound of formula (I) of the invention. There is also no prior art disclosure or indication that the properties claimed in claim 1 or shown in the specification as being possessed by the compound of formula (I) are inherent chemical or/and physical properties of the Andersag compounds. On the contrary, the prior art suggests that primaquine and its metabolites actually are more toxic, and that some metabolites are also completely non-functional.

For the reasons discussed above, it is respectfully submitted that the passing reference in Andersag to the usefulness of the genus of compounds described therein could not establish even a reasonable expectation of success with use of the recited compound in the claimed method.

c) The Evidence of Record Establishes a Long Felt Need for the Claimed Method

The evidence of record in the specification and in the literature references of record establish a long-felt need for a primaquine derivative that has anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of the prior art compound. The

Examiner has respectfully not addressed the evidence of unsolved need, which Applicants respectfully assert must be considered before a conclusion of obviousness can be reached (see, for example, *In re Piasecki*, 223 USPQ 785, 790 (Fed. Cir. 1984): "Evidence of secondary considerations may often be the most probative and cogent evidence in the record.").

The Examiner, while acknowledging that Appellant has recited the various advantages of the claimed compound over primaquine, has contended that Appellant has allegedly not recited advantages over the prior art compound. However, Appellant respectfully notes that the evidence of unsolved need of record subsumes the prior art compounds. For example, the Saxena et al article cited at page 3 of the Amendment dated December 5, 2000, states in pertinent part: "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system . . . ." In other words, the Saxena article, which was published 55 years after issuance of the Andersag patent, does not consider only primaquine as failing to solve a longstanding problem, but considers all of the prior art compounds (among which primaquine is considered to be the most prominent) as failing to solve the problem.

d) Separate Patentability of Claims 12, 13 and 16

The method of claim 16 is limited to one for combating malaria hypnozooites in the liver of an animal. The methods of claims 12 and 13 are limited to those that achieve a controlled delivery of the recited composition to, or the slow metabolic degradation of, the recited composition in an animal. Even assuming for the sake of argument that the reference were considered to show or suggest that the recited compound of formula 1 would be effective against

malarial parasites generally, it would not show or suggest these specific aspects of the claims. Andersag does not refer to any particular type of antimalarial activity.

e) Patentability of Claim 20

Claim 20 is directed to the process of preparing the recited product of formula 1. The process as claimed results in the easy isolation of the product without requiring vacuum distillation and simple crystallization provides a product of high pharmacopoeial standard. Since, as discussed above, the recited product of formula 1 cannot be considered to be obvious over Andersag, the claimed process is not shown or suggested by the prior art (see *In re Ochiai*, 37 USPQ 2d 1127 (Fed. Cir. 1995)).

CONCLUSION

In view of the above, it is respectfully submitted that claims 11-20 patentably distinguish over the cited art and a decision to that effect is respectfully requested.

Respectfully submitted,

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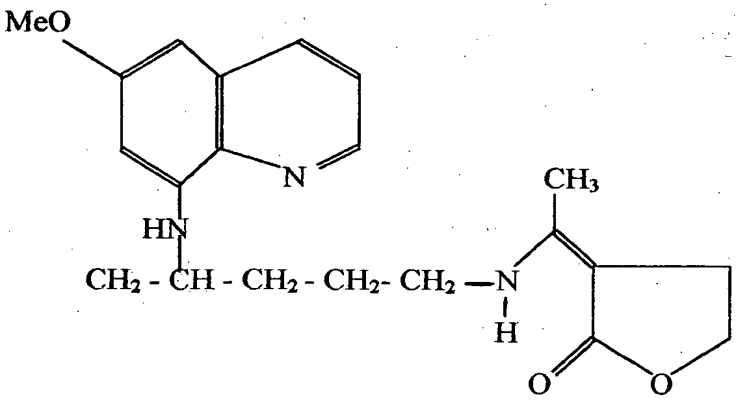
APPENDIX

Claim 11 A method for treatment of malaria in an animal comprising administering to the animal a primaquine compound of formula (1)



(1)

or a pharmaceutical composition containing said primaquine compound of formula (1), said compound having an enaminone functionality with gametocytocidal activity and low toxicity, said compound or composition being administered to the animal in a therapeutically effective amount for said treatment.

Claim 12 A method according to claim 11, wherein the composition is administered to the animal in an amount and manner effective to provide a controlled delivery thereof.

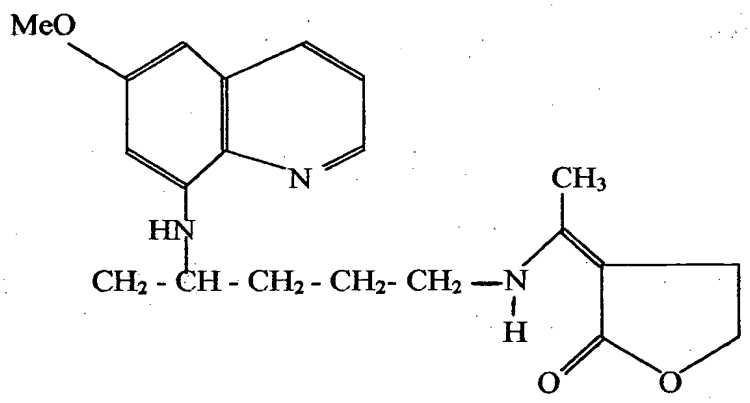
Claim 13 A method according to claim 11, wherein the composition is administered to the animal in an amount and manner effective to provide for slow metabolic degradation thereof in the animal.

Claim 14 A method according to claim 11, wherein the enaminone functionality provides

resistance to hydrolytic cleavage at acidic pH as compared to an enamine functionality.

Claim 15 A method according to claim 11, wherein the animal is a mammal.

Claim 16 A method for combating malaria hypnozooites in the liver of an animal which comprises administering a therapeutically effective amount of a compound of the formula



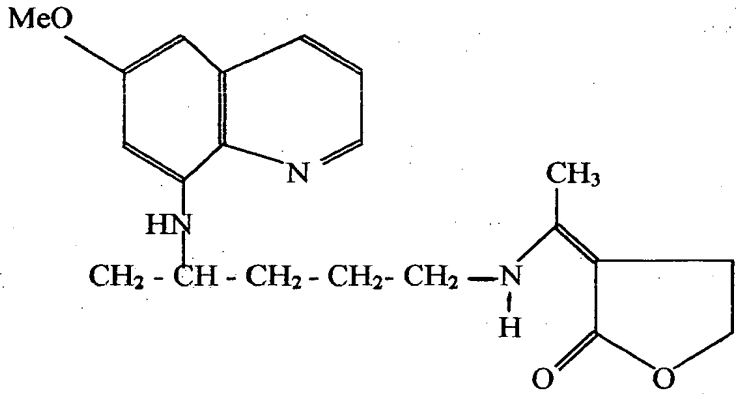
(1)

to an animal having said malaria hypnozooites present in the liver.

Claim 17 A method according to claim 16, wherein the compound has a high therapeutic index ratio in terms of methaemoglobin formation as compared to primaquine.

Claim 18 A method according to claim 16, wherein said compound causes substantially less oxidation of glutathione than does primaquine.

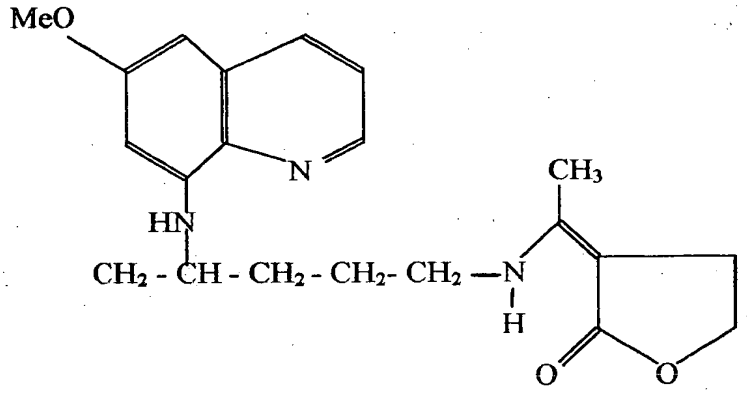
Claim 19 A method for treatment of malaria in a human comprising administering to the human a therapeutically effective amount of a primaquine compound of formula (1)



(1)

or a pharmaceutically composition containing said primaquine compound of formula (1), said compound having an enamione functionality with gametocytocidal activity and low toxicity.

Claim 20 A process for the preparation of a primaquine compound of formula (1)



(1)

comprising mixing 8-(4-amino-1-methylbutylamino)-6-methoxy quinoline with 3-acetyl-τ-butyrolactone in the presence of a base in respective amounts sufficient to form said compound.

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gametocytidal activity); and pages 15-16 and Tables IV-V on pages 21-23 (showing low toxicity)).

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a) Background

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As discussed in the specification, the claimed method satisfies the long-felt need for a solution to the problem. The specification shows an enhanced gametocytocidal activity of the claimed compound (see specification at pages 14 - 15 and Tables I - II) and a reduced toxicity in methaemoglobin and glutathione tests (see specification at pages 15 - 16 and Tables IV - VI). The specification thus shows the enhanced effectiveness of the claimed compound as compared with "the most important member of the 8-aminoquinoline group" (see Saxena et al excerpt above).

b) The Cited Art Does Not Establish a Case of *Prima Facie* Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in a reference or in the knowledge generally

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Appellant first notes that the cited reference, Andersag, does not describe the recited compound of formula 1. The Examiner acknowledges this, but argues that Andersag teaches a genus that encompasses the compound of formula 1 and includes, as one of twelve working examples, an example (Example 11) of the preparation of a specific compound that is allegedly structurally similar to the compound of formula 1. Example 11 describes the condensation of several different compounds, none of which results in the claimed compound. The closest compound described in Example 11 is the one described at page 2, second column, lines 45 - 48. This compound differs from the claimed compound in a number of significant respects. First, the cited compound has a pentane portion with the amino group in the 8 position of the amino functionality bound to a $CH(CH_3)$ group. By contrast, the reference compound would have the amino group in the 8 position of its amino functionality bound to a CH_2 group rather than to a $CH(CH_3)$ group. This would clearly affect the properties of this amino position. Moreover, the reference compound would have a lactone group with a beta methyl substituent that is lacking from the claimed compound.

ii) There is No Motivation to Modify the Reference

The Examiner nevertheless contends that Andersag provides motivation for one of ordinary skill in the art to modify the compound of Example 11 to arrive at the compound of formula 1 (and to use this compound in a method to treat malaria) because the reference allegedly teaches that any species within the disclosed genus would be effective in treating malaria. As discussed below, Appellant respectfully disagrees with the Examiner's contention that Andersag teaches that **any** species within the disclosed genus would be effective in treating malaria. Nevertheless, even assuming for the sake of argument that this contention were true, the reference would still not provide the required motivation to modify the compound of Example 11 as next discussed.

An indication that all compounds within a described genus would have antimalarial effects would not provide a motivation to select any particular compound from within the genus as opposed to any other. It certainly would not provide a motivation to substitute an amino-methyl-butyl- amino for an amino n-pentyl-amino or to remove a methyl from a butyrolactone as would be required to arrive at the compound of formula 1 from the reference compound. Indeed, if the inclusion of the reference compound in Example 11 were considered as an indication that such compound is one that is preferred, why would one of skill in the art have a motivation to replace or modify its substituents at all? Moreover, why would one of skill in the art be motivated to make the proposed substitutions as opposed to the myriad other substitutions that are possible within the framework of the generic formula described in Andersag and the other Andersag examples? The answer is that one of skill in the art would <u>not</u> be motivated to make these substitutions especially since Andersag's description relates generally to condensation

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In the absence of a motivation in the reference to select the recited compound of formula 1 from the vast number of compounds encompassed by the generic formula described therein, the reference cannot be considered to set forth even a *prima facie* case of obviousness (see *In re Baird*, 29 USPQ 2d 1550, 1552 (Fed. Cir. 1994)). The mere fact that the reference **can** be modified does not render the proposed modification obvious in the absence of a suggestion in the reference of the desirability of the modification (see *In re Mills*, 16 USPQ 2d 1430 (Fed. Cir. 1990); see also MPEP Section 2143.01).

iii) The Cited Art Does Not Provide a Reasonable Expectation of Success in the Claimed Method

Even assuming for the sake of argument that one of ordinary skill in the art would be motivated to modify the compound of Andersag Example 11 as contended by the Examiner, there still would not be a reasonable expectation of success in practicing the claimed method as would be required to establish a *prima facie* case of obviousness. In this connection, Appellant respectfully calls the Examiner's attention to the specification at pages 6 - 9, wherein the therapeutic activity and the toxicity of primaquine and its metabolites are discussed. The specification shows clearly the unpredictability in this art and the effect of small structural changes on the biological activity of primaquine and its derivatives. Given this unpredictability,

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reasonable expectation that it would be therapeutically effective in treating malaria with low toxicity. The salient points are as follows:

i) Andersag relates to condensation products of acetylbutyrolactones and primary amines of the aromatic and heteroaromatic series. The patent does not disclose any biological activity of the amines used or their toxicity. The only disclosure relates to the reaction with therapeutically useful amines.

ii) Primaquine, of which the compound of formula (1) of the invention is a derivative with an enamionone functionality, itself and its toxic metabolites were developed much subsequent to the Andersag Patent. The specification of the present application provides a detailed description of prior art which includes disclosure of primaquine and its toxic metabolites.

iii) Insofar as the Examiner's observations regarding the inherency of the gametocytocidal activity, low toxicity, controlled delivery facilitation, etc. are concerned, neither Andersag nor the aforementioned prior art described in the specification would provide even a reasonable expectation that putting enaminone at the terminal nitrogen atom would result in the slowing down of chain degradation, reduce methaemoglobin formation thereby lessening toxicity, or provide lower toxicity in terms of increased levels of glutathione. As is clear from the prior art, the high toxicity of primaquine affected its use as an antimalarial agent despite its otherwise demonstrable activity in terms of blood schizontocidal, tissue schizontocidal and gametocytocidal activity. The prior art metabolites of primaquine were either non-functional, or also responsible for its toxicity. The same would have been expected of the Andersag compounds.

iv) There is no teaching in the prior art that putting enaminone at the terminal nitrogen atom would lower the levels of oxidation of glutathione and reduce the levels of methaemoglobin formation thereby lessening toxicity.

v) Also, as is demonstrated in the specification on page 16, last paragraph, the use of primaquine *per se* causes drug induced haemolysis in persons deficient in G-6PD enzyme. The use of the compound of formula I of the invention, does not cause this result.

vi) The prior art does not show or suggest the enhanced or improved gametocytocidal activity of the compound of formula (I) of the invention. There is also no prior art disclosure or indication that the properties claimed in claim 1 or shown in the specification as being possessed by the compound of formula (I) are inherent chemical or/and physical properties of the Andersag compounds. On the contrary, the prior art suggests that primaquine and its metabolites actually are more toxic, and that some metabolites are also completely non-functional.

For the reasons discussed above, it is respectfully submitted that the passing reference in Andersag to the usefulness of the genus of compounds described therein could not establish even a reasonable expectation of success with use of the recited compound in the claimed method.

c) The Evidence of Record Establishes a Long Felt Need for the Claimed Method

The evidence of record in the specification and in the literature references of record establish a long-felt need for a primaquine derivative that has anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of the prior art compound. The

Examiner has respectfully not addressed the evidence of unsolved need, which Applicants respectfully assert must be considered before a conclusion of obviousness can be reached (see, for example, *In re Piasecki*, 223 USPQ 785, 790 (Fed. Cir. 1984): "Evidence of secondary considerations may often be the most probative and cogent evidence in the record.").

The Examiner, while acknowledging that Appellant has recited the various advantages of the claimed compound over primaquine, has contended that Appellant has allegedly not recited advantages over the prior art compound. However, Appellant respectfully notes that the evidence of unsolved need of record subsumes the prior art compounds. For example, the Saxena et al article cited at page 3 of the Amendment dated December 5, 2000, states in pertinent part: "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system . . . ." In other words, the Saxena article, which was published 55 years after issuance of the Andersag patent, does not consider only primaquine as failing to solve a longstanding problem, but considers all of the prior art compounds (among which primaquine is considered to be the most prominent) as failing to solve the problem.

d) Separate Patentability of Claims 12, 13 and 16

The method of claim 16 is limited to one for combating malaria hypnozooites in the liver of an animal. The methods of claims 12 and 13 are limited to those that achieve a controlled delivery of the recited composition to, or the slow metabolic degradation of, the recited composition in an animal. Even assuming for the sake of argument that the reference were considered to show or suggest that the recited compound of formula 1 would be effective against

malarial parasites generally, it would not show or suggest these specific aspects of the claims. Andersag does not refer to any particular type of antimalarial activity.

e) Patentability of Claim 20

Claim 20 is directed to the process of preparing the recited product of formula 1. The process as claimed results in the easy isolation of the product without requiring vacuum distillation and simple crystallization provides a product of high pharmacopoeial standard. Since, as discussed above, the recited product of formula 1 cannot be considered to be obvious over Andersag, the claimed process is not shown or suggested by the prior art (see *In re Ochiai*, 37 USPQ 2d 1127 (Fed. Cir. 1995)).

CONCLUSION

In view of the above, it is respectfully submitted that claims 11-20 patentably distinguish over the cited art and a decision to that effect is respectfully requested.

Respectfully submitted,

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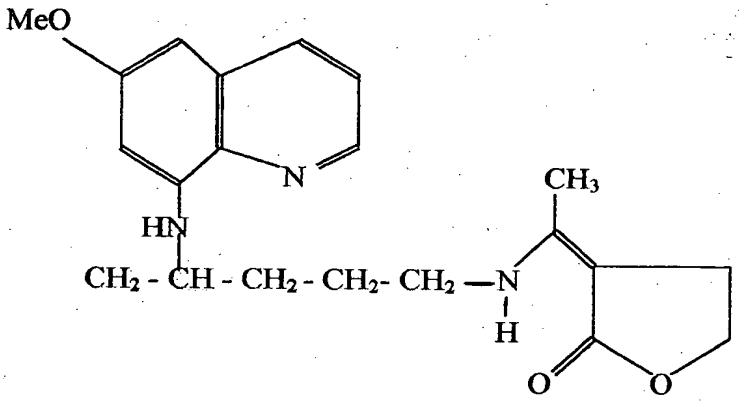
APPENDIX

Claim 11 A method for treatment of malaria in an animal comprising administering to the animal a primaquine compound of formula (1)



(1)

or a pharmaceutical composition containing said primaquine compound of formula (1), said compound having an enaminone functionality with gametocytocidal activity and low toxicity, said compound or composition being administered to the animal in a therapeutically effective amount for said treatment.

Claim 12 A method according to claim 11, wherein the composition is administered to the animal in an amount and manner effective to provide a controlled delivery thereof.

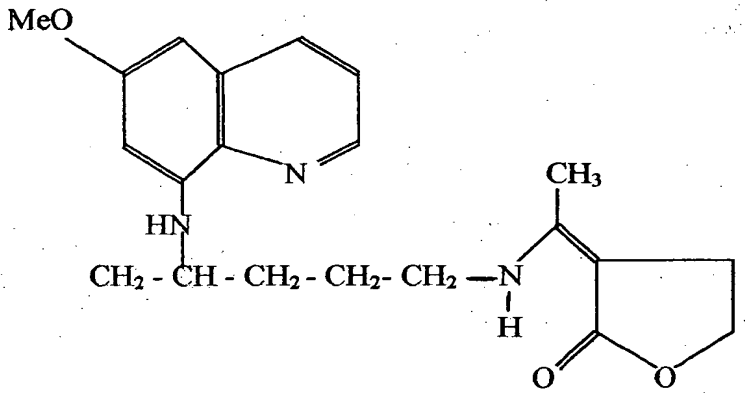
Claim 13 A method according to claim 11, wherein the composition is administered to the animal in an amount and manner effective to provide for slow metabolic degradation thereof in the animal.

Claim 14 A method according to claim 11, wherein the enaminone functionality provides

resistance to hydrolytic cleavage at acidic pH as compared to an enamine functionality.

Claim 15 A method according to claim 11, wherein the animal is a mammal.

Claim 16 A method for combating malaria hypnozooites in the liver of an animal which comprises administering a therapeutically effective amount of a compound of the formula



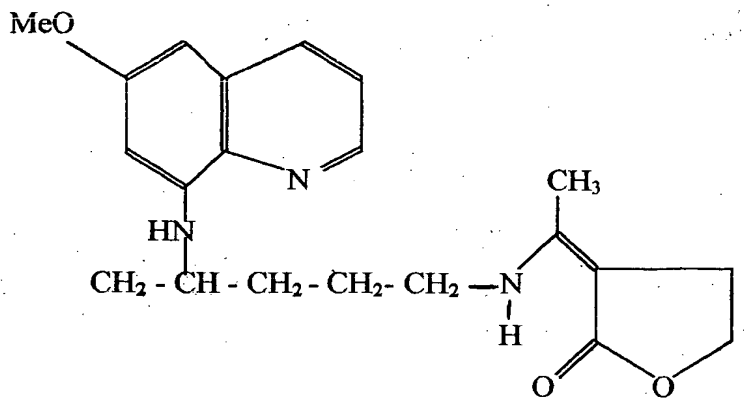
(1)

to an animal having said malaria hypnozooites present in the liver.

Claim 17 A method according to claim 16, wherein the compound has a high therapeutic index ratio in terms of methaemoglobin formation as compared to primaquine.

Claim 18 A method according to claim 16, wherein said compound causes substantially less oxidation of glutathione than does primaquine.

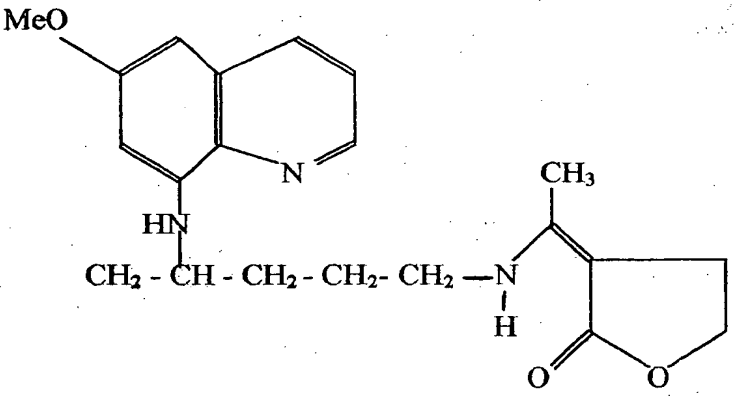
Claim 19 A method for treatment of malaria in a human comprising administering to the human a therapeutically effective amount of a primaquine compound of formula (1)



(1)

or a pharmaceutically composition containing said primaquine compound of formula (1), said compound having an enamione functionality with gametocytocidal activity and low toxicity.

Claim 20 A process for the preparation of a primaquine compound of formula (1)



(1)

comprising mixing 8-(4-amino-1-methylbutylamino)-6-methoxy quinoline with 3-acetyl-τ-butyrolactone in the presence of a base in respective amounts sufficient to form said compound.

#25

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ram PRATAP, et al

Serial No.: 09/316,313 Group No.: 1625

Filed: May 21, 1999 Examiner: E. Huang

For: METHOD FOR THE TREATMENT OF MALARIA BY THE USE OF PRIMAQUINE DERIVATIVE N^1-(3-ETHYLIDINOTETRAHYDR-2-ONE)-N^4-(6-METHOXY-8-QUINOLINYL)-1,4-P0ENTANEDIAMINE AS GAMETOCYTOCIDAL AGENT

Attorney Docket U-012254-3

Commissioner Patents and Trademarks
Washington, DC 20231

APPEAL BRIEF

Sir:

(1) Real Party in Interest

The real party in interest for this application is the Council of Scientific and Industrial Research, the assignee of the entire right, title and interest in and to this application.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, DC 20231

CLIFFORD J. MASS
Type or print name of person mailing paper)

Date: January 28, 2002

(Signature of person mailing paper)

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 11-20 have been finally rejected and are the subject of this appeal. Claims 1-10 and 21 were canceled previously.

(4) Status of Amendments

The amendment requested in the Amendment After Final filed 23 July 2001 has been entered, as courteously noted in the Advisory Action dated August 9, 2001. A Second Amendment After Final is being submitted simultaneously with this Appeal Brief and (obviously) has not been entered or considered on the record.

(5) Summary of Invention

The invention is a method for treatment of malaria or for combating malaria hypnozooites in the liver of an animal which comprises administering to an animal a therapeutically effective amount of the compound described in the specification at page 1, first full paragraph (identified as "the compound of formula 1") or a composition comprising the compound of formula 1. The compound has an enaminone functionality with gametocytocidal activity and low toxicity (see specification at page 11, last paragraph; pages 14-15 and Tables I and II on pages 18-20 (showing

gametocytidal activity); and pages 15-16 and Tables IV-V on pages 21-23 (showing low toxicity)).

(6) Issue

Whether claims 9-20 are unpatentable under 35 USC 103 over Andersag US Patent 2,187,847?

(7) Grouping of Claims

The claims do not stand or fall together. As discussed in Section (8) *infra*, claims 12 and 13 are separately patentable, and the claims depending from claim 16 are also separately patentable.

(8) Argument

a) Background

There has been a long-felt need for a primaquine derivative that has enhanced antimalarial activity and yet overcomes the longstanding problem posed by the toxicity of primaquine. In the present case, the evidence of record in the specification and in literature references cited of record establish a long-felt need for a primaquine derivative that has enhanced anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of primaquine. This problem is described in the specification of the present application at, for example, the paragraph bridging

pages 2 and 3 of the specification. Moreover, Appellant respectfully calls attention to the Saxena et al article cited in the Information Disclosure Statement dated November 1, 2000 which states in pertinent part:

> "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system such as induction of methaemoglobinaemia, haemolytic anaemia in G-6-PD deficient cases and toxicity in pregnant woman. Primaquine and other 8-aminoquinolines, are also known to produce oxidative stress, and inhibit various components of hepatic microsomal mixed function oxidase (MFO) system both *in vivo* and *in vitro*." (References omitted.)

Appellant also calls attention to the fact that the need for a solution to the problem exists more than sixty (60) years after issuance of the Andersag patent!

As discussed in the specification, the claimed method satisfies the long-felt need for a solution to the problem. The specification shows an enhanced gametocytocidal activity of the claimed compound (see specification at pages 14 - 15 and Tables I - II) and a reduced toxicity in methaemoglobin and glutathione tests (see specification at pages 15 - 16 and Tables IV - VI). The specification thus shows the enhanced effectiveness of the claimed compound as compared with "the most important member of the 8-aminoquinoline group" (see Saxena et al excerpt above).

b) The Cited Art Does Not Establish a Case of *Prima Facie* Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in a reference or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on an applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991). It is respectfully submitted that these criteria are not met in the present case, as discussed below.

i) The Cited Art Does Not Teach or Suggest All of the Claim Limitations

Appellant first notes that the cited reference, Andersag, does not describe the recited compound of formula 1. The Examiner acknowledges this, but argues that Andersag teaches a genus that encompasses the compound of formula 1 and includes, as one of twelve working examples, an example (Example 11) of the preparation of a specific compound that is allegedly structurally similar to the compound of formula 1. Example 11 describes the condensation of several different compounds, none of which results in the claimed compound. The closest compound described in Example 11 is the one described at page 2, second column, lines 45 - 48. This compound differs from the claimed compound in a number of significant respects. First, the cited compound has a pentane portion with the amino group in the 8 position of the amino functionality bound to a $CH(CH_3)$ group. By contrast, the reference compound would have the amino group in the 8 position of its amino functionality bound to a CH_2 group rather than to a $CH(CH_3)$ group. This would clearly affect the properties of this amino position. Moreover, the reference compound would have a lactone group with a beta methyl substituent that is lacking from the claimed compound.

ii) There is No Motivation to Modify the Reference

The Examiner nevertheless contends that Andersag provides motivation for one of ordinary skill in the art to modify the compound of Example 11 to arrive at the compound of formula 1 (and to use this compound in a method to treat malaria) because the reference allegedly teaches that any species within the disclosed genus would be effective in treating malaria. As discussed below, Appellant respectfully disagrees with the Examiner's contention that Andersag teaches that **any** species within the disclosed genus would be effective in treating malaria. Nevertheless, even assuming for the sake of argument that this contention were true, the reference would still not provide the required motivation to modify the compound of Example 11 as next discussed.

An indication that all compounds within a described genus would have antimalarial effects would not provide a motivation to select any particular compound from within the genus as opposed to any other. It certainly would not provide a motivation to substitute an amino-methyl-butyl- amino for an amino n-pentyl-amino or to remove a methyl from a butyrolactone as would be required to arrive at the compound of formula 1 from the reference compound. Indeed, if the inclusion of the reference compound in Example 11 were considered as an indication that such compound is one that is preferred, why would one of skill in the art have a motivation to replace or modify its substituents at all? Moreover, why would one of skill in the art be motivated to make the proposed substitutions as opposed to the myriad other substitutions that are possible within the framework of the generic formula described in Andersag and the other Andersag examples? The answer is that one of skill in the art would <u>not</u> be motivated to make these substitutions especially since Andersag's description relates generally to condensation

products of acetylbutyrolactones and primary amines of the aromatic and heteroaromataic series and not to enaminone derivatives of primoquine of the 8-aminoquinoline class. Appellant respectfully submits that Andersag provides no motivation to make the modification proposed by the Examiner.

In the absence of a motivation in the reference to select the recited compound of formula 1 from the vast number of compounds encompassed by the generic formula described therein, the reference cannot be considered to set forth even a *prima facie* case of obviousness (see *In re Baird*, 29 USPQ 2d 1550, 1552 (Fed. Cir. 1994)). The mere fact that the reference **can** be modified does not render the proposed modification obvious in the absence of a suggestion in the reference of the desirability of the modification (see *In re Mills*, 16 USPQ 2d 1430 (Fed. Cir. 1990); see also MPEP Section 2143.01).

iii) The Cited Art Does Not Provide a Reasonable Expectation of Success in the Claimed Method

Even assuming for the sake of argument that one of ordinary skill in the art would be motivated to modify the compound of Andersag Example 11 as contended by the Examiner, there still would not be a reasonable expectation of success in practicing the claimed method as would be required to establish a *prima facie* case of obviousness. In this connection, Appellant respectfully calls the Examiner's attention to the specification at pages 6 - 9, wherein the therapeutic activity and the toxicity of primaquine and its metabolites are discussed. The specification shows clearly the unpredictability in this art and the effect of small structural changes on the biological activity of primaquine and its derivatives. Given this unpredictability,

Appellant respectfully submits that one of skill in the art could not have had even a reasonable expectation from Andersag that the claimed compound (a) could be safely administered to a patient in any dosage, and (b) could be effective in treating the patient against malaria (see *Ortho Pharmaceutical Corp. v. Smith*, 22, USPQ 2d 1119, 1125 (Fed. Cir. 1992)).

The above is especially true in view of the limited disclosure in Andersag and the contradictory disclosure of the prior art as a whole. In this connection, it is axiomatic that each prior art reference must be evaluated as an entirety, and all of the prior art must be evaluated as a whole (see, e.g., *In re Evanega*, 44 USPQ 2d 1249 (Fed. Cir. 1987)). When considering Andersag as an entirety, it must be recognized that the reference contains only a passing reference to usefulness of the entire class of described compounds in the treatment of malaria. This does not mean, nor would it be taken by those of skill in the art to mean, that each and every compound within the described genus (nor even each and every compound exemplified in the patent) would be useful against malaria parasites. Moreover, the general statement of usefulness in the Andersag reference must be considered in the context of the prior art as a whole. As can be gleaned from the references cited in the specification at pages 6 - 9, and as discussed above, one cannot generalize as to the effectiveness or toxicity of primaquine or its derivatives. Indeed, the prior art when considered as a whole, teaches the opposite, i.e., generalization is impossible. Moreover, the evidence of unsolved need (discussed below) belies any implication that all compounds embraced by the Andersag genus would be useful to treat malaria.

Andersag does not discuss or even recognize differences between the biological activity or toxicity of any of the compounds described therein. When considered as a whole, the reference would not motivate one of skill in the art to make the recited compound with even a

reasonable expectation that it would be therapeutically effective in treating malaria with low toxicity. The salient points are as follows:

i) Andersag relates to condensation products of acetylbutyrolactones and primary amines of the aromatic and heteroaromatic series. The patent does not disclose any biological activity of the amines used or their toxicity. The only disclosure relates to the reaction with therapeutically useful amines.

ii) Primaquine, of which the compound of formula (1) of the invention is a derivative with an enamionone functionality, itself and its toxic metabolites were developed much subsequent to the Andersag Patent. The specification of the present application provides a detailed description of prior art which includes disclosure of primaquine and its toxic metabolites.

iii) Insofar as the Examiner's observations regarding the inherency of the gametocytocidal activity, low toxicity, controlled delivery facilitation, etc. are concerned, neither Andersag nor the aforementioned prior art described in the specification would provide even a reasonable expectation that putting enaminone at the terminal nitrogen atom would result in the slowing down of chain degradation, reduce methaemoglobin formation thereby lessening toxicity, or provide lower toxicity in terms of increased levels of glutathione. As is clear from the prior art, the high toxicity of primaquine affected its use as an antimalarial agent despite its otherwise demonstrable activity in terms of blood schizontocidal, tissue schizontocidal and gametocytocidal activity. The prior art metabolites of primaquine were either non-functional, or also responsible for its toxicity. The same would have been expected of the Andersag compounds.

iv) There is no teaching in the prior art that putting enaminone at the terminal nitrogen atom would lower the levels of oxidation of glutathione and reduce the levels of methaemoglobin formation thereby lessening toxicity.

v) Also, as is demonstrated in the specification on page 16, last paragraph, the use of primaquine *per se* causes drug induced haemolysis in persons deficient in G-6PD enzyme. The use of the compound of formula I of the invention, does not cause this result.

vi) The prior art does not show or suggest the enhanced or improved gametocytocidal activity of the compound of formula (I) of the invention. There is also no prior art disclosure or indication that the properties claimed in claim 1 or shown in the specification as being possessed by the compound of formula (I) are inherent chemical or/and physical properties of the Andersag compounds. On the contrary, the prior art suggests that primaquine and its metabolites actually are more toxic, and that some metabolites are also completely non-functional.

For the reasons discussed above, it is respectfully submitted that the passing reference in Andersag to the usefulness of the genus of compounds described therein could not establish even a reasonable expectation of success with use of the recited compound in the claimed method.

c) The Evidence of Record Establishes a Long Felt Need for the Claimed Method

The evidence of record in the specification and in the literature references of record establish a long-felt need for a primaquine derivative that has anti-malarial activity and yet overcomes the longstanding problem posed by the toxicity of the prior art compound. The

Examiner has respectfully not addressed the evidence of unsolved need, which Applicants respectfully assert must be considered before a conclusion of obviousness can be reached (see, for example, *In re Piasecki*, 223 USPQ 785, 790 (Fed. Cir. 1984): "Evidence of secondary considerations may often be the most probative and cogent evidence in the record.").

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d) Separate Patentability of Claims 12, 13 and 16

The method of claim 16 is limited to one for combating malaria hypnozooites in the liver of an animal. The methods of claims 12 and 13 are limited to those that achieve a controlled delivery of the recited composition to, or the slow metabolic degradation of, the recited composition in an animal. Even assuming for the sake of argument that the reference were considered to show or suggest that the recited compound of formula 1 would be effective against

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e) Patentability of Claim 20

Claim 20 is directed to the process of preparing the recited product of formula 1. The process as claimed results in the easy isolation of the product without requiring vacuum distillation and simple crystallization provides a product of high pharmacopoeial standard. Since, as discussed above, the recited product of formula 1 cannot be considered to be obvious over Andersag, the claimed process is not shown or suggested by the prior art (see *In re Ochiai*, 37 USPQ 2d 1127 (Fed. Cir. 1995)).

CONCLUSION

In view of the above, it is respectfully submitted that claims 11-20 patentably distinguish over the cited art and a decision to that effect is respectfully requested.

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APPENDIX

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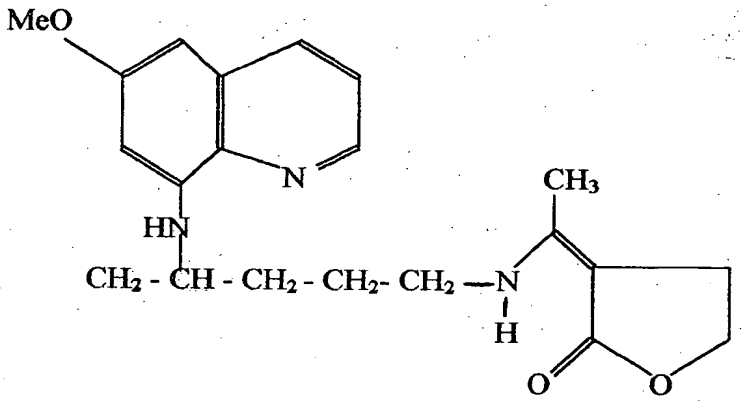

(1)

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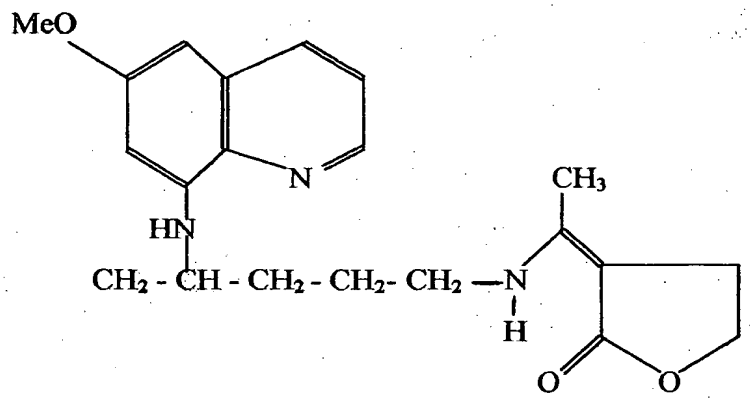
Claim 16 A method for combating malaria hypnozooites in the liver of an animal which comprises administering a therapeutically effective amount of a compound of the formula



(1)

to an animal having said malaria hypnozooites present in the liver.

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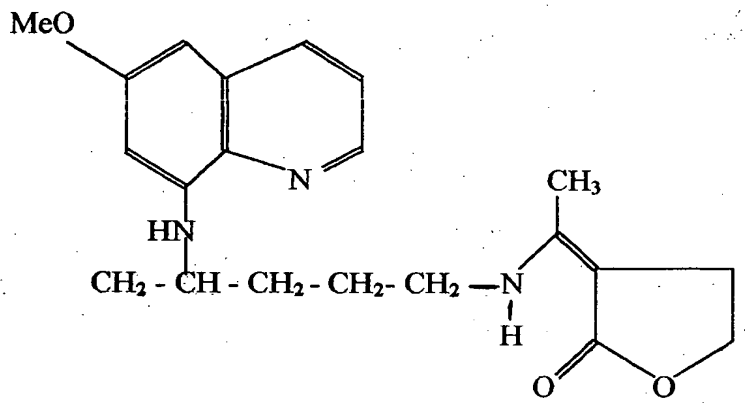

(1)

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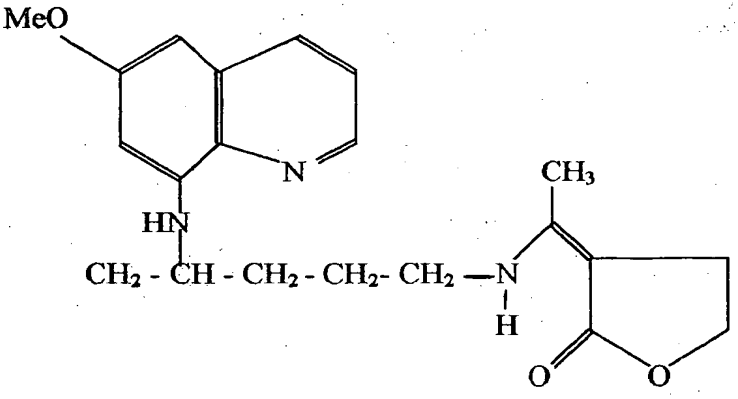

(1)

comprising mixing 8-(4-amino-1-methylbutylamino)-6-methoxy quinoline with 3-acetyl-τ-butyrolactone in the presence of a base in respective amounts sufficient to form said compound.